

II. REMARKS

Claims 1-116 are presently pending in this application. Claims 1-30 and 82-116 have been withdrawn pursuant to a restriction requirement. Claims 31-33, 48, 56 and 65-81 stand variously rejected under 35 U.S.C. §§ 103 and 112. Claims 33-47, 49-55 and 57-64 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Support for the amendments to the claims can be found throughout the specification and claims as originally filed, for example, on page 73, line 33. The amendments are made solely to advance prosecution and are in no way intended as an admission as to the correctness of the Examiner's positions. No new matter has been added to the application by way of the amendment.

Rejections Under 35 U.S.C. § 103(a)

Claims 31-33, 48, 56 and 64-81 stand rejected as allegedly unpatentable over Wong (Wong et al. J. Investigative Medicine 43(2) supp. 2 p. 397A (1995)) and Mehta (U.S. Patent No. 5,308,750), in view of Hoogenboom (WO 93/06213) and Chanock (Chanock et al. Infectious Agents and Disease 2:118-131 (1993)).

The Basis of the Rejection

Applicants again request clarification of the basis of this rejection, pursuant to the MPEP (i.e., the guide to Patent Office procedure) which requires the Office to make clear the basis of their rejections and point to the relevant parts of the reference so that an applicant is given fair opportunity to respond. See, MPEP 706.02(j). Despite the refusal to clarify the rejection or to point to specific, relevant passages within the references, Applicants address below what they believe the rejection to be.

A prima facie case of Obviousness Has Not Been Established

In order to establish a *prima facie* case of obviousness the Office must show three things: (1) motivation within the references to arrive at the claimed invention; (2) a reasonable expectation of success and (3) that the combination of references teaches each and every limitation of the claims. Each requirement is discussed in detail below.

Applicants traverse the rejection because, regardless of what combination, the cited references do not teach or suggest the claimed invention.

1) There is no Motivation Within the References to Make the Suggested Changes

In order to establish a case of obviousness, the Office must show that there is a suggestion or motivation within the references that would lead a skilled artisan to modify (or combine) the references to arrive at the claimed invention. The Federal Circuit has repeatedly held that using "hindsight reconstruction" to provide the necessary motivation is improper. (see, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Napier* 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) stating that "obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some teaching, suggestion or incentive supporting the combination.")¹. In addition, the art must suggest the desirability of the modification. (See, e.g., *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984), emphasis added, holding that "the mere fact that the prior art could be so modified would not have the modification obvious unless the prior art suggested the desirability of the modification"). In the pending case, there is no motivation to combine the references as suggested by the Office.

The Office Action asserts that the motivation to arrive at the claimed invention is

¹Applicants note again that *In re McLaughlin*, cited by the Examiner allegedly supporting hindsight reconstruction to support an obviousness rejection, is not a Federal Circuit decision. Therefore, the holding of this case is not controlling. More recent case law on this topic is cited above.

found within Mehta and/or Wong. (Office Action, pages 4-5). In particular, with regard to Mehta, it is alleged that "clear" motivation derives from the fact "that there is no difficulty in obtaining monoclonal antibodies to that antigen." (Office Action, page 5). For its part, Wong is alleged to provide "clear motivation to create human Fab fragments in order to test the same theories in human situations." (Office Action, page 4). The Office Action does not reference specific passages of Wong or Mehta and, indeed, there are no such passages because neither references suggest the desirability of the claimed invention -- nucleic acid molecules encoding human Fabs. It is insufficient for the Office to assert that the teachings of the referenced could be modified to arrive at the claimed invention when the proper standard is demonstrating that the cited references suggest the desirability of modifying their disclosures to arrive at the claimed invention. For the reasons detailed below, the cited references do not suggest the desirability of such modifications.

Mehta is directed to mouse monoclonal antibodies that bind to HCV E2/NS1. Mehta does not teach or suggest human antibodies and does not teach isolated nucleic acid molecules encoding monoclonal Fab molecules. Indeed, the only Fab molecules discussed in Mehta are polyclonal, namely Fab dimers derived from IgG molecules purified from individuals seropositive for antibodies to HCV proteins. (Mehta, col. 11, lines 6-10). Moreover, Mehta does not teach any nucleic acid sequences for the murine monoclonal antibodies -- the sequences in the sequence listing represent HCV peptide sequences (see, Mehta, Example 1 for SEQ ID NOs 1-6, and Example 6 for SEQ ID NOs 7-10). The claimed invention is directed to human antibodies. Thus, any teachings regarding the ease or difficulty of making mouse monoclonals are not relevant. There is nothing in Mehta that would suggest to one of skill in the art that the claimed invention would be desirable.

Wong's abstract deals with murine monoclonal antibodies to Hepatitis C Virus E2 envelope protein and discusses that these antibodies may be involved with blocking HCV

penetration into cells (last sentence of the Abstract). As in Mehta, there is simply no teaching or suggestion in Wong concerning an isolated nucleic acid molecule encoding a human Fab molecule that exhibits immunological binding affinity for a hepatitis C virus E2 antigen. Accordingly, there is no suggestion to arrive at the claimed invention.

Thus, there is no teaching or suggestion within Mehta or Wong that would lead one of skill in the art to the claimed invention.

2) No Reasonable Expectation of Success

The second requirement that must be met by the Office is to show that the proposed modification of the references had a reasonable expectation of success, determined from the vantage point of the skilled artisan the time the invention was made. (*See, e.g., Amgen v. Chugai*, 18 USPQ2d 1016 (Fed. Cir. 1991)). In moving from the prior art to the claimed invention, the Office cannot base a determination of "expectation of success" on what the skilled artisan might "try" or find "obvious to try." *In re Dow*, 5 USPQ2d 1529 (Fed. Cir. 1988).

Mehta and Wong are directed to mouse monoclonal antibodies and neither teach or suggest isolated nucleic acid molecules encoding human antibodies. Hoogenboom is completely inapplicable as it discloses only **humanized** murine antibodies and is silent as to the claimed **human** monoclonal antibodies. Thus, to find the requisite reasonable expectation of success, the Office appears to be relying on the teachings of Chanock, which is cited as disclosing "technology useful in creating human monoclonal antibody fragments." (Office Action, page 4). The Examiner's reliance on this reference is misplaced. Chanock is silent as to HCV or E2 antigens. Moreover, Chanock provides evidence as to unresolved difficulties involved in making human antibodies, for example, lack of information concerning heavy-light chain pairing (page 122, second paragraph), the unpredictability of the usefulness of human antibodies in preventing or treating disease (page 124-126) and the preference for whole IgG over Fabs (page 128, right hand

column). Thus, one skilled in the art would not have had a reasonable expectation that human Fabs that exhibit binding affinity for an HCV E2 antigen could be produced. Further, it is improper for the Office to assert that Chanock's disclosure of general methods makes the claimed invention "obvious to try", especially in light of the problems associated with the Chanock procedure. Thus, the combination of references does not provide the skilled artisan with the requisite reasonable expectation of success.

3) The Claimed Limitations are Not Suggested by the Combination of References

The third requirement which must be met by the Office is to show that the combination of references teaches or suggests all the limitations of the claims. *See, e.g., In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). The claims must also be considered as a whole and "focusing on the obviousness of substitutions and differences instead of on the invention as a whole ... [is] a legally improper way to simplify the difficult determination of obviousness." *Hybritech v. Monoclonal Antibodies Inc.*, 231 USPQ 81 (Fed. Cir. 1986). As with the first and second requirements, this third requirement has not been met.

As a whole, the claims are directed to nucleic acids encoding specific human Fabs that exhibit immunological binding affinity for a HCV E2 antigen. The combination of cited references does not teach or suggest this claimed invention. In particular, Mehta and Wong do not disclose any of the claimed elements, as these references are limited to disclosure of mouse antibodies and are silent as to human monoclonal Fabs and nucleic acids encoding these molecules. Hoogenboom does not set forth methods for production of recombinant human antibodies. Chanock also fails to describe or demonstrate nucleic acids encoding Fabs that exhibit binding affinity to HCV E2. The Office appears to be focusing on individual components of the invention, mixing and matching these components from the prior art and concluding that the invention would have been obvious. This is an improper application of the law governing 103 rejections.

In sum, the Office has not established a *prima facie* case of obviousness and withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 31-33, 48, 56 and 64-81 remain rejected as allegedly containing subject matter that was not described in the specification so as to convey to one skilled in the art that Applicants were in possession of the claimed subject matter. The Examiner maintains that Applicants have not adequately described the claimed molecules. (Office Action, page 5).

Applicants traverse this rejection.

Contrary to the Examiner's assertion, the written description requirement of section 112 does not require that the claims be limited in scope to those sequences disclosed in SEQ ID Nos. Indeed, in *Fiers v. Revel*, cited in the Office Action, the Federal Circuit indicated that, although disclosure of a method of isolating DNA did not adequately describe the DNA, the DNA itself may be properly defined by one or more of the following parameters: "structure, formula, chemical name or physical properties." Thus, it is possible that DNA can be entirely described by its physical properties, *i.e.* by function.

In a recent synthesis of applicable case law (including *The Regents of the University of California v. Eli Lilly*, cited on page 7 of the Office Action), the Patent Office has issued Interim Guidelines on Written Description which state, in part:

"... Office personnel should review the entire specification, including specific embodiments, figures, sequence listings, and the claims, to understand what applicant has invented and the correspondence between what applicant described, *i.e.*, had possession of, and what applicant is claiming. ... if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function. ... in well developed arts, [these] identifying characteristics are sufficient for a skilled artisan to recognize applicant had possession of the species ...

to reasonably predict sufficient identifying characteristics of other members of the genus and, thus, establish possession of the genus." (emphasis, added)

The Interim Guidelines regarding Written Description also provide, in Section D(2), the following exemplary claim and supporting facts:

"A monoclonal antibody which specifically binds to the novel cancer associated TAG-31 antigen but which does not substantially bind normal adult human tissues, wherein said monoclonal antibody has a binding affinity of greater than 3 times $10^9 M^{-1}$ for TAG-31.'

Considering the claim as a whole, it is drawn to a genus of monoclonal antibodies. Although the specification does not disclose the complete structure of a representative number of species to support the claimed genus of antibodies, it does disclose multiple monoclonal antibodies which have the isotype claimed as well as the binding specificity and binding affinity characteristics recited in the claims. In this well-developed art, additional identifying characteristics for a substantial portion of the genus are well-known (e.g., number of chains, disulfide bonds, constant and variable regions, etc.). Thus, applicant's disclosure combined with what was known in the art are sufficient to describe the claimed genus of monoclonal antibodies in such full, clear, concise and exact terms to show applicant was in possession of the claimed antibodies. Thus, the claim meets the D(2) criteria."

Applying these rules to the instant application, Applicants submit that the specification more than adequately describes the claimed invention. The disclosure contains much more than a "potential method for isolating" the claimed nucleic acids. In fact, the specification teaches both methods of isolating suitable nucleic acids (e.g., Examples 1-4), expression and testing of the polypeptide products for antigenicity (e.g., Examples 5 and 9-12) and, in addition, the precise sequence of multiple Fabs isolated by these methods. Ample structure (e.g., SEQ ID Nos:) and identifying characteristics (e.g., specified binding affinity for HCV E2) of the molecules are provided so that a skilled artisan would recognize that Applicants were in possession of the claimed invention. Thus, one skilled in the art would readily recognize from this disclosure that Applicants were in possession of the claimed invention.

The Office's analysis of the exemplary generic claim to monoclonal antibodies which are characterized by their binding affinity provides still further evidence that the pending claims (which have been amended to specify binding affinity) are adequately described. Sequence identification numbers are not required to describe a claimed molecule. The Office makes it clear that the development of antibodies is a "well-developed art." Moreover, the Guidelines indicate that specifying binding affinity is sufficient to describe antibodies such as Fabs. Thus, the pending claims more than adequately describe the claimed nucleic acids and Fabs encoded thereby.

In sum, the rejections under section 112, first paragraph are improper and Applicants respectfully request these rejections be withdrawn.

III. CONCLUSION

In view of the foregoing, Applicant submits that the claims are now in condition for allowance and requests early notification to that effect.

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Date: Nov 19, 1999

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